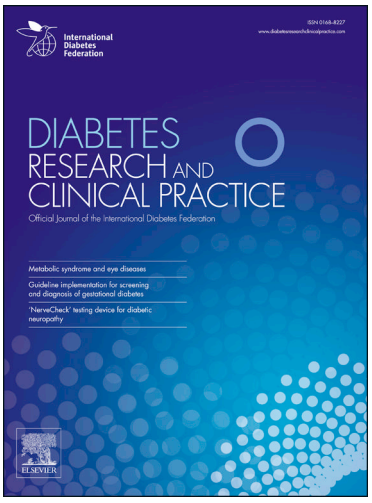

Exenatide twice-daily does not affect renal function or albuminuria compared to titrated insulin glargine in patients with type 2 diabetes mellitus: a *post-hoc* analysis of a 52-week randomised trial

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ORIGINAL RESEARCH PAPER

Exenatide twice-daily does not affect renal function or albuminuria compared to titrated insulin glargine in patients with type 2 diabetes mellitus: a *post-hoc* analysis of a 52-week randomised trial

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Running title: Renal effects of exenatide vs insulin glargine

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ABSTRACT

Aims: To compare effects of long-term treatment with GLP-1RA exenatide twice-daily versus titrated insulin glargine (iGlar) on renal function and albuminuria in type 2 diabetes (T2DM) patients.

Methods: We *post-hoc* evaluated renal outcome-data of 54 overweight T2DM patients (mean±SD age 60±8years, HbA1c 7.5±0.9%, eGFR 86±16mL/min/1.73m^2, median[IQR] urinary albumin-to-creatinine-ratio (UACR) 0.75 [0.44-1.29]mg/mmol) randomised to exenatide 10µg twice-daily or titrated iGlar on-top-of metformin for 52-weeks. Renal efficacy endpoints were change in creatinine clearance (CrCl) and albuminuria (urinary albumin-excretion [UAE] and UACR) based on 24-hour urines, collected at baseline and Week-52. eGFR and exploratory endpoints were collected throughout the intervention-period, and after a 4-week wash-out.

Results: HbA1c-reductions were similar with exenatide (mean±SEM -0.80±0.10%) and iGlar (-0.79±0.14%; treatment-difference 0.02%; 95%CI -0.31 to 0.42%). Change from baseline to Week-52 in CrCl, UAE or UACR did not statistically differ; only iGlar reduced albuminuria (P<0.05;within-group). eGFR decreased from baseline to Week-4 with exenatide (-3.9±2.1mL/min/1.73m^2;P=0.069) and iGlar (-2.7±1.2mL/min/1.73m^2;P=0.034), without treatment-differences in ensuing trajectory. Exenatide versus iGlar reduced bodyweight (-5.4kg; 2.9 to 7.9;P<0.001), but did not affect blood pressure, lipids or plasma uric acid.

Conclusions: Among T2DM patients without overt nephropathy, one-year treatment with exenatide twice-daily does not affect renal function-decline or onset/progression of albuminuria compared to titrated iGlar.

Key Words: GLP-1 receptor agonist, exenatide, insulin glargine, albuminuria, glomerular filtration rate, diabetic kidney disease, renoprotection, type 2 diabetes mellitus

Trial registration: Clinicaltrials.gov ID: NCT00097500

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1 | INTRODUCTION

Diabetic kidney disease (DKD) is the most common cause of chronic- and end-stage kidney disease, and increases patients' risk of cardiovascular events and premature death.(1) DKD manifests clinically as albuminuria, impaired glomerular filtration rate (GFR), or both.(1) Intensified control of modifiable renal risk factors, and use of renin-angiotensin-system (RAS)-inhibitors, slows albuminuria progression and preserves renal function in at-risk patients with type 2 diabetes (T2DM). Nevertheless, residual renal risk remains high, and the absolute number of patients with DKD continues to rise in parallel with the T2DM-pandemic.(1)

Glucagon-like peptide (GLP)-1 receptor agonists (RAs) are effective and well-tolerated glucose-lowering drugs for the treatment of T2DM.(2) GLP-1RAs harbour a minimal hypoglycaemia-risk, often induce weight-loss, and are associated with modest reductions in blood pressure (BP) and circulating lipids.(1) Interestingly, GLP-1RAs were reported to prevent histological features of DKD in pre-clinical models, and improve renal biomarkers in placebo-controlled clinical trials *"beyond glycaemic control"*.(3) Three cardiovascular outcome-trials (CVOTs; ELIXA, LEADER and SUSTAIN-6) demonstrated that GLP-1RA-therapy, on top of standard-of-care, reduces onset and progression of albuminuria in high-risk T2DM patients during 2-4 years of follow-up.(4-7) In LEADER, liraglutide modestly slowed estimated GFR (eGFR)-decline compared to placebo at Month-36.(6)

Mechanisms underlying the *glucose-independent* renoprotective properties of GLP-1RAs in T2DM remain uncertain. Proposed pathways comprise: 1) *direct* GLP-1R-mediated effects on the diabetic kidney (e.g. natriuresis and amelioration of glomerular hyperfiltration), and 2) *indirect* benefits via improvements in renal risk-profile (both classical factors [obesity, hypertension, dyslipidaemia] and emerging factors [e.g. plasma uric acid (PUA), oxidative-stress/inflammation]).(1,3) In order to carefully evaluate GLP-1RA-specific benefits on renal outcomes in RCTs, confounding effects of glucose-lowering *per-se* should be minimalised by warranting glycaemic-equipoise between treatment-arms. Notably, in all CVOTs of GLP-1RAs published to date, treatment-differences in HbA1c were likely of clinical relevance in terms of reducing DKD-risk (time-averaged mean change from baseline ~0.3-1.1%-points).(3) In ELIXA, the favourable effect of lixisenatide on progression of urinary albumin-to-creatinine ratio (UACR) in all patients was attenuated (P=0.07) after correction for small HbA1c-differences(4), suggesting an –at least partially– mediating effect of glucose-lowering.

Thus, long-term intervention trials in T2DM that evaluate renal outcomes should ensure glycaemic-equipoise, preferably using head-to-head comparator designs, to justly assess benefits *"beyond glycaemic control"*, and enhance clinical relevance. In this *post-hoc* analysis of a 52-week RCT(8), we evaluated whether the short-acting GLP-1RA exenatide twice-daily slows renal function-decline and onset and progression of albuminuria compared to titrated insulin glargine (iGlar) in T2DM patients inadequately controlled on metformin.

2 | MATERIALS AND METHODS

2.1 | Design, participants and interventions

This is a *post-hoc* analysis of a randomised, open-label, active-comparator, parallel-group trial, performed at three study sites in Sweden, Finland and the Netherlands. The trial was originally designed to determine treatment-effects on clamp-measured beta-cell function after 52-weeks;

detailed design and methods were published previously.(8) In brief, 69 Caucasian T2DM patients (male and female, age 30-75 years, HbA1c 48-80 mmol/mol [6.5-9.5%], BMI 25-40 kg/m^2) were randomised in a 1:1 ratio to receive exenatide twice-daily (N=36; Byetta®, AstraZeneca, London, UK) or titrated iGlar (N=33; Lantus®, Sanofi, Paris, France) for 52 weeks in addition to stable and ongoing metformin monotherapy (titration schemes in Appendix-S1). All patients in current analysis attended a follow-up visit 4 weeks after the last administration of the investigational-product, to explore reversible drug-effects. The study protocol was approved by the ethics committee at each participating centre, registered at ClinicalTrials.gov (NCT00097500), and was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

2.2 | Study endpoints

The primary renal efficacy endpoints for this analysis were change from baseline to Week-52 in creatinine clearance (CrCl) and urinary albumin excretion (UAE), both determined from 24-hour urine-collections. Participants were given oral and written instructions on how to collect a 24-hour urine-sample, and were instructed to postpone collection in case of fever, urinary-tract infection, or menstruation, and to refrain from strenuous exercise during the collection-period. Patients were advised to store the 24-hour urine-collections in dedicated containers, in the refrigerator for a maximum of 2 days prior to assay. We considered 24-hour urine-collections to be inadequate if 24-hour urine creatinine-excretion was <10 or <8mg/kg of lean body mass (LBM; measured by DEXA-scan, as described(9)) in men and women, respectively. CrCl is expressed as uncorrected-values, and BSA-standardised. Serum and urinary-creatinine and urinary-albumin were measured in a central laboratory by standard procedures.

Secondary renal efficacy endpoints were change in UACR from baseline to Week-52, and changes in eGFR over time. Fasting serum creatinine was used to calculate eGFR using the MDRD Study-equation. Difference between groups in the average rate of change in eGFR for three specified time-periods were quantified; from baseline to Week-4 (period-1; to assess immediate treatment-effects, expectedly of renal haemodynamic-nature), from Week-4 to Week-52 (period-2; to assess long-term treatment-effects); from Week-52 to Week-56 (period-3; to assess reversible, conceivably haemodynamically-mediated, treatment-effects). Exploratory endpoints included trajectories and time-averaged means (both absolute values and deltas) of HbA1c, fasting plasma glucose (FPG), fasting-BP, fasting lipids and PUA.

2.3 | Statistical analyses

All statistical analyses were performed using SPSS Statistics for Windows, V22.0 (IBM Corp., Armonk, NY), and done according to a statistical analysis plan agreed before data-inspection. Multivariable linear regression models were used to examine exenatide- compared to iGlar-induced effects after 52-weeks; corresponding baseline-values were added as independent variables to correct for potential between-group differences pre-treatment. Within-group comparisons over specific time-periods were analysed using paired *t*-tests (for Gaussian-distributed data) or Wilcoxon signed rank tests (non-Gaussian distributed data), as appropriate. Absolute and incremental/decremental time-averaged mean differences in risk factors were calculated, and analysed using independent samples *t*-tests.

Pearson's and Spearman correlation analyses, as appropriate, were performed to explore individual associations between renal endpoint-data and time-averaged mean changes from baseline in prespecified risk factors. All P-values are from two-sided tests of the null hypothesis; an α-level of 0.05 was regarded as statistical significant. Data are reported as mean ±SEM, median [interquartile range], baseline-corrected mean treatment-difference (95% confidence interval; CI), or frequency (%).

3 | RESULTS

3.1 | Study population

Fifty-five of the 69 randomised patients collected 24-hour urines at both the pre-treatment and final *on-drug* (Week-52) visit. In one patient (1.8%; randomised to exenatide), urine-collection was considered inadequate, and as such, a total of 54 patients are included in current analysis (evaluable population; Appendix-S2). Demographic and baseline clinical characteristics were well-balanced between groups (Table). In addition to metformin, all patients used other drugs at baseline, mostly antihypertensive drugs (RAS-inhibitors 53.7%, diuretics 20.3%, beta-blockers 35.2%, calcium-channel blockers 14.8%), statins (50.0%), and platelet-aggregation-inhibitors (44.4%). Numerically fewer patients randomised to exenatide (N=12; 46.2%) compared to iGlar (N=17; 60.7%) used RAS-inhibitor-therapy before enrolment. During the course of the study, iGlar dose was 19.2±1.4 units/day at Week-4, reaching a plateau of 34.9±3.6 units/day at Week-52.

3.2 | Effects on renal efficacy-endpoints

At baseline, none of the patients had CrCl <60 mL/min/1.73m^2, and 13.7% (N=7; 2 randomised to exenatide, 5 randomised to iGlar) were categorized to have microalbuminuria (UAE >30 mg/24-hour or UACR ≥3 mg/mmol). None of the patients had macroalbuminuria (UAE>300 mg/24-hour or UACR ≥30 mg/mmol). CrCl did not change in either treatment-group from baseline to Week-52 (Figure-1A, Appendix-S3); mean±SEM change was -3.7±5.1 mL/min/1.73m^2 with exenatide (P=0.473; baseline 103.3±5.1 mL/min/1.73m^2) and -1.3±5.6 mL/min/1.73m2 with iGlar (P=0.821; baseline 108.1±5.5 mL/min/1.73m^2); baseline-adjusted treatment-difference -5.2 (95% CI -18.9 to 8.6; P=0.451) mL/min/1.73m^2. UAE and UACR remained unaffected with exenatide, and were significantly reduced from baseline to Week-52 with iGlar (P<0.05 for both); baseline-corrected risk-ratios did not reach statistical significance (Figures-1B/1C, Appendix-S3). One patient in the exenatide-arm progressed from normo- to microalbuminuria from baseline to Week-52, while two patients allocated to iGlar regressed from micro- to normoalbuminuria. Change in urine volume/24-hours tended to decrease with exenatide (-249±129 mL; P=0.065), and increase with iGlar (191±110 mL; P=0.094); baseline-adjusted treatment-difference -427 mL (-750 to -103 mL; P=0.011). Treatment-differences in overall eGFR-trajectory (Figure-1D), and rate of change in eGFR for the three specified time-periods (Figure-1E) were not observed. From baseline to Week-4 (period-1), there was a short-term decrease in eGFR in the iGlar-group (P=0.034) and exenatide-group (P=0.069); P>0.05 for between-group comparisons. During chronic administration (period-2; from Week-4 to Week-52), eGFR remained stable with exenatide, and tended to increase with iGlar (P=0.092). After cessation of study-drugs (period-3; Week-52 to follow-up visit Week-56), eGFR remained unchanged (P>0.05). There were no adverse events (AEs) reflecting potential acute renal failure with either treatment.

3.3 | Effects on renal risk-factors

Changes in renal risk-factors are shown in Figure-2 and Appendix-S3. HbA1c (baseline 7.5±0.9%;58±10mmol/mol) decreased in both groups (P<0.001); at Week-52, HbA1c was reduced by 0.80±0.10%;%;-9±1mmol/mol with exenatide and 0.79±0.14%%;-9±1mmol/mol with iGlar (baseline-corrected treatment-difference 0.02% [95% CI -0.31 to 0.42; P=0.749). Both treatments decreased FPG from baseline to Week-52 (-1.48±0.30 mmol/L with exenatide, -3.05±0.42 mmol/L with iGlar); treatment-difference 1.90 mmol/L (95% CI 1.25 to 2.56; P<0.001). Bodyweight at baseline was 91.9±13.9 kg; by Week-52, exenatide-treated patients achieved weight-loss of 4.1±0.8 kg, versus a non-significant gain of 1.3±1.0 with iGlar (treatment-difference -5.4 (95% CI -7.9 to -2.87; P<0.001). No within- or between-group differences were seen in BP and PUA after 52-weeks. Exenatide decreased LDL-cholesterol (-0.30±0.12; P=0.023) from baseline to Week-52, but no significant treatment-differences in lipids were observed. Absolute time-averaged mean and delta FPG-levels differed between-groups in favour of iGlar (P≤0.001), while time-averaged mean change from baseline in bodyweight favoured exenatide (P<0.001); no other between-group differences in time-averaged means or deltas were observed (Appendix-S4).

3.4 | Exploratory correlation-analyses

Correlation-analyses between changes in renal-endpoints and time-averaged changes in renal risk-factors are presented in Appendix-S5. In the entire cohort, changes in CrCl were negatively correlated with changes in PUA (r=-0.303, P=0.031), driven by those on iGlar (r=-0.499, P=0.009). Changes in UAE and UACR correlated positively with changes in HbA1c, FPG and systolic-BP (Appendix-S5). In the iGlar-group, changes in UAE and UACR correlated positively with systolic-BP (both P<0.05), while UACR was non-significantly correlated with HbA1c (r=0.369, P=0.076). In the exenatide-group, changes in UACR correlated with systolic-BP (r=0.496, P=0.022) and non-significantly with PUA (r=-0.405, P=0.068), while changes in UAE tended to correlate with LDL-cholesterol (r=0.373, P=0.088).

4 | DISCUSSION

In this *post-hoc* analysis, among metformin-treated T2DM patients without overt nephropathy, one-year treatment with exenatide twice-daily does not affect 24-hour CrCl, albuminuria or eGFR-trajectory compared to titrated iGlar. Correlation-analyses suggested that individual albuminuria-lowering effects were driven by changes in systolic-BP for both treatments, while HbA1c-lowering may have contributed to the modest UACR-improvement with iGlar.

Secondary and exploratory analyses of three landmark CVOTs indicated that short- and long-acting GLP-1RAs (lixisenatide(4,5), liraglutide(6) and semaglutide(7)) slow progression of albuminuria compared to placebo in patients with T2DM and moderate-to-high cardiovascular risk. Importantly, subsequent mediation-analyses suggested that renal benefits were (at least in-part) glucose-*independent*.(4,5,10) A placebo-controlled, cross-over trial in 32 patients with T2DM and persistent albuminuria also concluded that the observed 32% UACR-reduction with liraglutide was partly glucose-*independent*.(11) In LEADER, liraglutide slowed eGFR-decline by 2% compared to placebo after 36-months of follow-up (-7.44 vs -7.82 mL/min/1.73m^2, respectively).(6) Although cardiovascular-safety of the extended-release (once-weekly) formulation of exenatide was demonstrated in

EXSCEL(12), renal outcome data of this CVOT are still eagerly awaited. Not all placebo-controlled trials showed favourable effects of GLP-1RAs on albuminuria and estimated/measured GFR(3,13-15), and some controversy regarding the renoprotective efficacy of this drug-class remains. As microvascular complications are related to HbA1c-levels, and *post-hoc* mediation-analyses can only speculate about mechanisms driving the result, suggestions of renoprotection "beyond glycaemic control" require confirmation in dedicated trials that safeguard glycaemic-equipoise.

As a result of the use of an active comparator-arm (iGlar) in current study, long-term differences in HbA1c between treatments were minimal (0.02%), and direct comparison between two relevant glucose-lowering drug-choices to intensify metformin is possible. The neutral effect of exenatide on renal-endpoints in our head-to-head RCT are in line with a 2014 observational study, that examined historical data from electronic medical-records in routine US-practice.(16) That study also showed no differences between exenatide twice-daily and iGlar in change in renal function or albuminuria at 1-year in T2DM patients typically without nephropathy. In contrast, exenatide twice-daily vs glimepiride resulted in greater 24-hour UAE-reductions in microalbuminuric T2DM patients after 26-weeks.(17) Integrated data from dulaglutide registration trials indicated lower UACRs upon treatment with this long-acting GLP-1RA than with iGlar and other active comparators in 6005 T2DM patients, with and without CKD.(18) Fewer patients on dulaglutide compared to iGlar experience a 40%-decline in eGFR at any point during the one-year treatment-period.(18) Finally, in the 52-week AWARD-7 trial, eGFR was higher with dulaglutide compared to iGlar at end-of-trial, without between-group differences in albuminuria, in 577 patients with T2DM and moderate-to-severe CKD.(19) The discrepant effects of GLP-1RA-therapy on renal endpoints are incompletely understood, but may relate to pharmacokinetic/-dynamic differences between compounds (short-acting vs long-acting GLP-1RAs) and/or studied T2DM populations (non-CKD vs CKD-patients).(3)

Numerous mechanisms by which GLP-1RAs may improve renal outcomes are postulated(1,3). First, as GLP-1R-expression has been reported in various locations in the kidney(3), *direct* actions of GLP-1RAs on renal physiology were expected. Indeed, GLP-1RA-administration induces natriuresis and diuresis in healthy males(20) and T2DM patients(21-23), attributed to blockade of sodium-hydrogen exchange in the proximal tubule.(3) Through the consequent increased sodium-delivery to the distally located macula densa, GLP-1RAs could –in keeping with sodium-glucose co-transporter (SGLT)2-inhibitors– activate tubuloglomerular feedback (TGF), leading to pre-glomerular vasoconstriction and a resulting decrease in glomerular hyperfiltration.(24) Such renal vasomodulatory effect would cause an acute decrease in GFR, followed by a smaller decline in renal function during continued treatment, as described with RAS-inhibitors and SGLT2-inhibitors.(1,24,25) Interestingly, in the current trial, both exenatide and iGlar-treated patients displayed such a pattern of change in renal function (i.e. a small [~3.5%] short-term decrease, followed by eGFR-stabilization), suggestive of an acute reduction in intraglomerular-pressure.(24) Although similar suggestive falls in eGFR were seen promptly after liraglutide-treatment (13,14,26), these changes did not differ from placebo, and were quantitatively smaller than those seen upon RAS- and SGLT2-inhibition.(24) Consistent, mechanistic-studies in humans that used gold-standard methodology to assess renal haemodynamics in the fasting(14,21,22) and postprandial(23) state, also indicate that GLP-1RAs harbour a neutral, or more

variable, effect on measured-GFR, effective renal plasma-flow and estimated intraglomerular-pressure in T2DM patients. Moreover, in contrast to reports on RAS- and SGLT2-inhibitors(24), we did not observe a reversible change in eGFR after discontinuation of either study-drug that would suggest involvement of a haemodynamic-mechanism. Acute changes in eGFR seen with exenatide and iGlar in current study may likely be the result of glucose-lowering *per-se*. Notably, renal haemodynamic actions of GLP-1RAs do not *only* involve TGF-activation, but are likely more complex (e.g. involving GLP-1R-mediated vasodilation of pre-glomerular arterioles [opposing a TGF-mediated vasoconstrictive-response] and *indirect* vasomodulatory actions on postglomerular-arterioles) and may vary between individuals. Second, modest benefits of GLP-1RAs on the renal risk-profile in T2DM are also hypothesised to *indirectly* contribute to their renoprotective efficacy.(1) However, in current study, and despite reductions in bodyweight and LDL-cholesterol in the exenatide-group, the pleiotropic effects of GLP-1RA-therapy did not translate into a glucose-independent benefit on renal endpoints. Although drug-effects on bodyweight and cholesterol have been shown to be relevant in reducing patients' renal risk(1), other off-target effects (including unfavourable actions) of GLP-1RAs in individual patients should also be taken into account, and may offset any theorised renoprotection. Notably, all renal risk variables in current analysis were assessed in the fasting state, and may as such not fully reflect the *net* risk of the individual patient over 24-hours (i.e. involving ingestion of multiple meals). To illustrate, short-acting GLP-1RAs (exenatide twice-daily and lixisenatide) may on the one hand have a sustained favourable effect on meal-induced dysglycaemia, dyslipidaemia and inflammatory/oxidative-stress markers in T2DM patients (27), but may on the other hand –and in contrast to long-acting GLP-1RAs– increase postprandial-BP compared to insulin.(23,28) It is tempting to speculate that 24-hour integrated pleiotropic effects (i.e. the ratio of favourable/unfavourable effects in both the fasting and postprandial state) differ between short- and long-acting GLP-1RAs, and may in part help explain dissimilarities between compounds in glucose-independent effect on renal and other outcomes. Comparative studies that generate an integrated risk score (such as the PRE-score(29)) upon treatment with GLP-1RAs with different pharmacokinetic profiles are needed to explore this principle in detail. Finally, we observed a notable correlation between albuminuria-lowering and time-averaged decrements in fasting-BP with exenatide, which is in line with one of the suggested anti-albuminuric drivers of liraglutide-treatment(11), and reveals an individual responder-characteristic in terms of renoprotection with this GLP-1RA.

As GLP-1RAs are associated with nausea, vomiting, diarrhoea and acute natriuresis and increased diuresis(2,3), concerns arose around volume-related renal safety issues (i.e. acute kidney injury) in prone T2DM patients.(30) Our results, as well as data from retrospective and large-sized prospective registration studies(3,15), do not confirm 11 early-reported cases of exenatide-induced acute interstitial nephritis and tubular necrosis.(30) Interestingly, we did find an intriguing reduction in 24-hour urine-output of ~425 mL after 52-weeks of exenatide versus iGlar. This is in line with our previous observation that exenatide-infusion reduces urinary-flow, free water-clearance and fractional urea-excretion in T2DM patients.(21)

Our study has some limitations that merit consideration. First, this was a *post-hoc* analysis of an RCT that was not originally designed to assess treatment-effects on renal-variables. Our results can

therefore only be interpreted as hypothesis-generating. Second, the external validity (generalizability) is limited by the nature of the participants studied (i.e. those with preserved/normal renal function and typically no albuminuria); potential renal benefits of GLP-1RAs may be seen particularly in those patients with more advanced-CKD.(6) Third, CrCl and UAE using 24-hour urine-collections are susceptible to variation and collection errors. To enhance quality of our 24-hour urine-collection results, participants were rigorously instructed on the procedure, and data of likely undercollectors (based on *expected* daily creatinine-excretion given DEXA-scan-measured LBM) were excluded.

In conclusion, among T2DM patients without overt nephropathy, one-year treatment with exenatide twice-daily did not affect renal function-decline or onset and progression of albuminuria compared to iGlar, despite modest benefits on patients' renal risk-profile. Long-term renal outcome studies that compare GLP-1RAs with different pharmacokinetic-profiles, and use relevant active comparators, in T2DM patients with more advanced CKD are needed to further assess the suggested *glucose-independent* renoprotective efficacy of this drug-class.

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AUTHOR CONTRIBUTION STATEMENT

M.H.A.M. researched data, wrote the manuscript, and contributed to the discussion. M.C.B. collected and researched data, contributed to the discussion, and reviewed/edited the manuscript. L.T. and D.H.vR. researched data, contributed to the discussion, and reviewed/edited the manuscript. R.J.H., H.Y.-Y., and J.A.J. reviewed/edited the manuscript. A.C. and B.E. collected data and reviewed/edited the manuscript. M.D. was involved in the development of the study protocol, and initial discussion of the data. M.H.A.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

CONFLICTS OF INTEREST:

M.H.A.M. is a consultant and speaker for Eli Lilly & Co., Sanofi and Novo Nordisk (all honoraria are paid to employer; the VU University Medical Center). M.C.B. and R.J.H. are employees and stockholders of Eli Lilly & Co. During the study, M.C.B. and R.J.H. were employed at the VU University Medical Center, Amsterdam. H.Y.-J. serves as a consultant for Amylin Pharmaceuticals. Through H.Y.-J., the Helsinki University Central Hospital has received research grants from Amylin Pharmaceuticals, Inc., and Eli Lilly & Co. B.E. reports personal fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., Merck Sharp & Dohme, Mundipharma, Navamedic, Novo Nordisk, Sanofi and RLS Global, outside the submitted work. Before her passing in 2014, M.D. was a consultant and speaker for Eli Lilly & Co. Through M.D., the VU University Medical Center, Amsterdam, received research grants from Amylin Pharmaceuticals, and Eli Lilly & Co. L.T. consulted for Eli Lilly & Co. D.H.vR. serves on advisory boards for AstraZeneca, Merck Sharp & Dohme, Novo Nordisk and Sanofi (all honoraria are paid to employer; the VU University Medical Center). No other potential conflicts of interest relevant to this article were reported.

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TABLE | Demographic and baseline characteristics

Characteristic	**Exenatide BID** N=26	**Insulin glargine** N=28	**P-value**
Female sex, N (%)	10 (38.5)	7 (25.0)	0.287
Age, years	59.7 ±8.1	59.4 ±7.5	0.853
Bodyweight, kg	90.1 ±14.1	93.5 ±13.8	0.375
Body Mass Index, kg/m^2	30.4 ±4.1	30.4 ±3.7	0.988
Daily metformin dose, mg	1795 ±708	1591 ±786	0.366
Diuretic use, N (%)	5 (19.2)	6 (21.4)	0.841
RAS-inhibitor use, N (%)	12 (46.2)	17 (60.7)	0.284
ACE-inhibitor, N (%)	10 (38.5)	9 (32.1)	0.627
ARB, N (%)	2 (7.7)	8 (28.6)	0.048
Beta-blocker use, N (%)	8 (30.8)	11 (39.3)	0.513
Calcium channel blocker use, N (%)	4 (15.4)	4 (14.3)	0.910
Statin use, N (%)	9 (34.6)	18 (64.3)	0.029
Platelet-aggregation inhibitor use, N (%)	11 (42.3)	13 (46.4)	0.761
HbA1c, %	7.53 ±0.98	7.45 ±0.77	0.748
HbA1c, mmol/mol	58 ±10	58 ±8	0.748
Fasting plasma glucose, mmol/L	9.39 ±1.83	9.02 ±2.03	0.486
Total cholesterol, mmol/L	4.94 [4.19-5.55]	4.75 [4.14-5.61]	0.749
HDL-cholesterol, mmol/L	1.13 [1.01-1.41]	1.17 [1.04-1.38]	0.952
LDL-cholesterol, mmol/L	3.04 [2.61-3.52]	2.80 [2.29-3.53]	0.279
Triglycerides, mmol/L	1.63 [1.29-2.44]	2.29 [1.54-3.07]	0.119
Systolic-BP, mmHg	136 ±13	136 ±14	0.955
Diastolic-BP, mmHg	81 ±8	80 ±6	0.877
Heart rate, mmHg	69 ±12	71 ±10	0.624
eGFR, mL/min/1.73m^2	84.7 ±17.0	87.8 ±14.9	0.473
Albumin excretion rate, mg/24h	7.36 [5.91-15.14]	10.90 [7.12-19.56]	0.263
Albumin-creatinine ratio, mg/mmol	0.63 [0.41-1.27]	0.77 [0.54-1.79]	0.477
Microalbuminuria, N (%)	2 (7.7)	5 (17.9)	0.318

Data are presented as mean±SD, median [inter-quartile range] or N (%). Albuminuria status at baseline was unavailable in 3 patients randomised to exenatide twice-daily and 1 patient randomised to insulin glargine. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; BID, twice-daily; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RAS, renin-angiotensin-system.

FIGURE 1│ Change from Baseline to Week-52 in urinary albumin excretion (**A**; median IQR), creatinine clearance (**B**; mean ±SEM) and urinary albumin-creatinine ratio (**C**; median IQR). Mean ±SEM changes in estimated glomerular filtration rate (eGFR) over time (**D**), and during pre-specified time-periods (**E**).

FIGURE 2│ Change in renal risk factors over time